REMARKS

I. Claim Status

Claims 14, 19, 20, 25, 55, 56, 72, 75 and 93-120 are pending and under examination.

Claims 99, 105, 109 and 113 that were rejoined by the Examiner have been amended to delete "bispecific antibody" and "artificial antibody," as previously done for other claims. Accordingly, claims 99, 105, 109 and 113 are entitled to the priority date of provisional application 60/041,850, filed April 9, 1997. All pending claims are thus entitled to the priority date of the aforementioned provisional application.

Claims 117-120 have been cancelled.

All claim amendments and cancellations are made without prejudice or disclaimer as to any cancelled subject matter.

By this Amendment, no new matter has been added to the application.

II. Duplicate Claims

The Examiner had warned that claims 113-116 were substantial duplicates of claims 117-120, respectively. In response, claims 117-120 have been cancelled.

III. Response to Rejections Under 35 U.S.C. §103(a)

The obviousness rejections set forth in the Office Action are summarized and addressed as follows.

Claims 14, 19, 20, 25, 55, 56, 93-98 and 105-108 are rejected as allegedly obvious over Becker et al., EP 0613 007 ("Becker") and further in view of Audia et al., U.S. Patent No. 5,965,614. ("Audia"). The rejection is traversed on the grounds that the Examiner has failed to properly construe Becker and Audia, and as a result has failed to establish a proper factual basis for a rationale to modify and/or combine Becker and Audia. In view of these failures, it is apparent that Examiner has improperly used the specification of the instant specification and hindsight reconstruction to construct the present rejection.

Claims 14, 19, 20, 25, 55, 56, 93-98 and 105-108 are not obvious over Becker and further in view of Audia because, when properly construed, the prior art would not provide the

required rationale for modifying Becker and/or combining Becker and Audia, nor would the prior art provide the required reasonable expectation of success that Becker could be modified or combined with Audia to arrive at the claimed invention. Nor is such a rationale to be found in the general knowledge among those of ordinary skill in the art. Accordingly, the Examiner has not established a prima facie case that the claims are obvious over Becker and Audia.

"During examination, the examiner bears the initial burden of establishing a prima facie case of obviousness." *In re Kumar,* 418 F.3d 1361, 1366 (Fed. Cir. 2005). In so doing, the Examiner must make the factual determinations set forth in *Graham v. John Deere Co.,* 383 U.S. 1, 17 (1966): (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations of nonobviousness, if any. "Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant." *In re Rijckaert,* 9 F.3d 1531, 1532 (Fed. Cir. 1993) (citations omitted).

Claims are likely to be unobvious "when the prior art teaches away" from their practice. *KSR,* 550 U.S. at 416. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Kahn,* 441 F. 3d 977, 990 (Fed. Cir. 2006) (*quoting In re Gurley,* 27 F.3d 551, 553 (Fed. Cir. 1994)). A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.,* 721 F.2d 1540, 1550 (Fed. Cir. 1983); *In re Hedges,* 783 F.2d 1038, 1041 (Fed. Cir. 1986) ("[T]he prior art as a whole must be considered. The teachings are to be viewed as they would have been viewed by one of ordinary skill."). It is thus, "impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.'" *Id.* (*quoting In re Wesslau,* 353 F.2d 238, 241 (CCPA 1965)).

In the setting out the instant rejection, the Examiner erred in failing to consider the prior art, in particular the primary reference Becker, as a whole. Becker is directed to anti-Aβ antibodies that are specific for Aβ having particular secondary structure, i.e., conformation. The

overwhelming majority of the disclosure of Becker is concerned with anti-Aβ antibodies that are specific for Aβ which is predominantly in a β-sheet conformation. *See*, Becker at, e.g., Abstract, col. 1, lines 52-colulmn 2, line 9. Becker thus states:

> This invention describes a series of assays useful in evaluating the efficacy of agents which inhibit the neurotoxic effects of β-amyloid peptide. These assays employ β-amyloid peptide which is predominantly β-sheet conformation.
>
> In another embodiment, this invention describes antibodies having a specificity for β-amyloid peptide which is predominantly in a β-sheet conformation. These antibodies show poor reactivity with β-amyloid peptide which has a high degree of random coil or α-helix secondary structure.
>
> This invention also encompasses pharmaceutical formulations comprising an antibody having specificity for β-amyloid peptide which is predominantly in a β-sheet conformation in combination with a parenterally-administratable medium.

Column 1, lines 52-column 2, line 9.

Becker further states:

> The results of these neurotoxicity experiments [described in the prior art] demonstrates there is a direct correlation between the degree of β-sheet structure in the β-amyloid peptide and its neurotoxicity. There is minimal neurotoxicity associated with those samples of β-amyloid peptide that that have a high degree of random coil in their secondary structure.
>
> The use, therefore, of β-amyloid peptide which has adopted a predominantly β-sheet conformation allows the development of compounds which specifically inhibit the neurotoxicity.

Column, 5, lines 27-42.

> In addition to being functional as direct therapeutic and diagnostic aids, the availability of a family of antibodies which are specific for β-amyloid peptide in

> the β-sheet conformation enables the development of numerous assay systems for detecting agents which bind to β-amyloid peptide in this specific formation.

Column 7, line 53-column 8, line 1.

These passages illustrate that a fair reading of Becker, taken as a whole, is that anti-Aβ antibodies that are specific for Aβ in the β-sheet conformation might be used in diagnostic and therapeutic methods. Becker contains no suggestion that antibodies other than those that are conformationally-specific for Aβ in the β-sheet conformation might be useful as a therapeutic agent. To the extent that Becker discloses anti-Aβ antibodies that are specific for Aβ that is predominantly in an α-helix or random coil conformation, one of ordinary skill in the art would understand that such antibodies might be used as a reagent in assays for agent that inhibit the neurotoxicity of β-amyloid peptide. *See*, e.g., claim 3 and 5. Upon reading Becker, however, one of ordinary skill in the art would understand, that such antibodies would not be suitable as Alzheimer's disease therapeutics, because Becker states explicitly that there is "minimal neurotoxicity" associated with the Aβ conformation that is recognized by the antibodies. Becker at column, 5, lines 30-33. ("There is minimal neurotoxicity associated with those samples of β-amyloid peptide that that have a high degree of random coil in their secondary structure.")

Becker's disclosure that antibodies specific for Aβ in a predominantly β-sheet conformation may be useful as a therapeutic whereas antibodies specific for Aβ in a random coil conformation would not be useful as a therapeutic is consistent with the state of the art at the time the instant application was filed. Soto et al., for example, discloses that Aβ peptides exist as either "amyloidogenic conformers" and "non-amyloidogenic conformers." Soto et al., *Biochem. J* (1996), 701-701, *see,* e.g., Abstract. ("Soto," copy enclosed with an IDS submitted herewith). Soto performs experiments to determine the fibrillogenic potential of different Aβ peptides and conformers and concludes:

> [S]ynthetic peptides containing the sequence 1-40 and 1-42 of Aβ and several Aβ analogues are composed of a mixture of two major species: one is highly amyloidogenic, partly resistant to proteolysis and contains a β-sheet structure; the other is poorly

> amyloidogenic, sensitive to proteolysis and adopts mainly a random coil conformation.
>
> * * *
>
> Although recent findings indicate a variability between lots in the relative levels of Aβnac and Aβac found with synthetic peptides of Aβ(1-40), it was always clear that there was a direct correlation between the secondary structure of the peptide and its fibrillogenic and protease resistance properties.

Soto at page 705, section entitled DISCUSSION, paragraph bridging columns 1 and 2.

Both Becker and Soto thus make it clear that it is the β-sheet conformation of Aβ that is the pathogenic form of Aβ and that antibodies that recognize the β-sheet conformation of Aβ would be useful as therapeutics, but that antibodies that do not recognize the β-sheet conformation of Aβ, in particular, antibodies that recognize soluble Aβ having a predominantly random coil conformation would not be useful as a therapeutic antibody. This flatly contradicts the present invention.

In view of the teachings in Becker and the state of the art, there would have been no reason for one of ordinary skill to combine Becker and Audia to arrive at the claimed invention because there is no indication that the 3D6 antibody disclosed in Audia recognizes the β-sheet conformation of Aβ.

The Examiner's offered rationale for using the 3D6 antibody is not well taken because it relies on a mistaken factual finding concerning Becker. The Examiner thus states that "Becker teaches antibodies that bind to dissociated (i.e., soluble Aβ, including Aβ1-40) and those that bind to aggregated Aβ, wherein administration of both types of antibodies is therapeutically effective in treating the neurotoxicity associated with Alzheimer's disease (col. 2, lines 38-50; col. 5, lines 42-50; col. 7, lines 49-52), as in [the pending claims]." Office Action at page 4. In providing the rationale for combining Becker and Audia, the Examiner thus concludes, "Becker teaches that administration of any Aβ antibody would be useful to treat Alzheimer's disease." Office Action at page 6, lines 15-16.

The sections of Becker cited by the Examiner, however, do not support the Examiner's assertion that Becker teaches "any" antibody to Aβ would be useful for the treatment of Alzheimer's disease. The text at col. 2, lines 38-50 of Becker merely discusses the use of, e.g., Aβ1-40 in the "following examples." The text at col. 5, lines 42-50 discloses that antibodies may be obtained that are specific for either the β-sheet or random coil or α-helix conformation. Neither of these passages makes any reference to the use of any antibody for therapeutic use. The text at col. 7, lines 49-52 reads, "The antibodies of the present invention are especially preferred in the diagnosis and/or treatment of Alzheimer's disease in mammals, preferably humans." This passage makes no reference to any particular antibody. However, when taken in the context of Becker's explicit disclosure that "[t]here is minimal neurotoxicity associated with those samples of β-amyloid peptide that that have a high degree of random coil in their secondary structure" and Becker's repeated disclosure that antibodies specific for the β-sheet conformation of Aβ are useful as therapeutic agents, it is clear that it would *not* be "especially preferred" to use "any" antibody to treat Alzheimer's disease. To the contrary, Becker makes it clear that only antibodies that are specific for the β-sheet conformation of Aβ are useful as therapeutic agents. When properly construed as a whole, Becker thus provides no factual basis to support the Examiner's conclusion that Becker discloses that "any" antibody to Aβ would be useful for treating Alzheimer's disease.

Becker teaches away from the claimed invention because a person of ordinary skill in the art "would be led in a direction divergent from the path that was taken by the applicant" (*In re Kahn,* 441 at 990), in that following Becker would lead to treating Alzheimer's disease with Aβ antibodies that specifically recognize the insoluble, β-sheet conformer of Aβ, whereas the instant claims call for free-end specific antibodies that recognize soluble Aβ, which has a predominantly random coil conformation.

Nor does Audia cure the defect in the Examiner's offered rationale for combining Becker and Audia to arrive at the claimed invention. Audia mentions the 3D6 antibody only in the context of a β-amyloid sandwich assay. Audia at column 49, lines 10-27. Audia makes no mention of using any antibody to treat Alzheimer's disease. Audia provides no rationale for using the 3D6 antibody in methods for treating Alzheimer's disease.

In short, the stated factual underpinning for the rationale to combine Becker and Audia (that Audia teaches using "any" antibody treat Alzheimer's disease) is mistaken. In the absence of this mistake, neither Becker nor Audia, either alone or in combination provides any rationale to arrive at the claimed methods of using the free-end specific antibodies that are targeted to a free N-terminus of Aβ or a free C-terminus of Aβ1-40 and that bind to soluble Aβ in CSF. For at least this reason, the rejection based on Becker and Audia should be withdrawn.

Additionally, the Examiner's selective reading of Becker and subsequent piecing-together of elements from Becker and Audia establish that the Examiner has used the instant specification to arrive at the motivation to combine the prior art to arrive at the claimed invention. The Examiner, for example, states "[t]he skilled artisan would have been motivated to use the 3D6 antibody, i.e., which is a free end specific antibody directed to the N-terminus of Aβ, in Becker's therapeutic methods because Audia teaches that said antibody is highly specific for Aβ and does not cross react with other closely associate molecules, such as APP." Office Action at 6. The Examiner, however, fails to point to any evidence that before the filing of the instant application one of ordinary skill in the art would have had any reason to believe it was desirable to use an antibody that recognized the Aβ peptide but did not recognize APP for treating Alzheimer's disease. In contrast, the instant specification discloses the importance of treating Alzheimer's disease with free-end specific antibodies, e.g.:

> This exquisite sensitivity of free-end specific antibodies is required so as not to affect the normal biological functions of the transmembrane receptor-like APP molecule that is implicated in several important physiological roles (such as mediation in adhesion, growth promoting effects, neuroprotection, neuritic outgrowth, recycling of synaptic vesicles, regulation of apoptosis inhibition of serine proteases, receptor and signal transduction functions, calcium metabolism and nucleic acid transcription). Thus, in one embodiment, the invention utilizes free-end specific antibodies to inhibit the accumulation of amyloid β peptides, to ameliorate or prevent the neurotoxic consequences of amyloid deposition, to slow Alzheimer's Disease or other diseases characterized by amyloid β deposition progression or to delay their onset.

Specification at page 16, lines 15-25.

Nor does the Examiner provide any support for his conclusion that it would have been obvious to use a monoclonal antibody that binds to Aβ that is soluble in the CSF. Becker and Soto represent the state of the art when the application was filed, which held that the pathogenic agent in Alzheimer's disease was neuritic plaques containing insoluble, deposited Aβ. In contrast to the prior art, the instant specification sets forth the importance of targeting soluble Aβ that is present in the CSF:

> In another embodiment, the pharmaceutical composition and the antibodies of the present invention will delay the onset and inhibit or suppress the progression of Alzheimer's Disease by having a peripheral effect. The clearance or the removal of the amyloid beta from the periphery will change the equilibrium of the amyloid beta in the blood and as a result in the brain. Recent studies have shown that amyloid beta is transported from the cerebrospinal fluid to the plasma with an elimination half-life from brain of about half an hour. Thus, the antibody can affect the amyloid beta level in the plasma, cause accumulation of central amyloid beta in the plasma and as a result reduce the amyloid Aβ deposition in the brain.

Specification at page 15, lines 13-21.

It is axiomatic that the Examiner may "not use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch,* 972 F.2d 1260, 1266 (Fed. Cir. 1992) (internal citations omitted). It is improper, in determining whether a person of ordinary skill would have been led by the combination of references, simply to "[use] that which the inventor taught against its teacher." *In re Lee,* 277 F.3d 1338, 1343 (Fed. Cir. 2002), *citing W.L. Gore v. Garlock, Inc.,* 721 F.2d 1540, 1553 (Fed. Cir. 1988) ("[t]here must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from the applicant's disclosure").

In KSR, the Supreme Court cautioned that "[a] factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of argument reliant upon ex post

reasoning." *KSR,* 550 U.S. at 421 (*citing Graham v. John Deere Co.,* 383 U.S. 1, 36 (1966)). "[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l. Co. v. Teleflex Inc.,* 550 U.S. 398, 418 (2007), *quoting In re Kahn,* 441 F.3d 977, 988 (Fed. Cir. 2006). "'[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" *Id.* The Court stated:

> [I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does . . . because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.

Id. at 418-419; *see also id.* at 418 (requiring a determination of "whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue").

Here, the Examiner fails to correctly identify any reason why one of ordinary skill in the art would combine elements of the prior art to arrive at the claimed invention. Instead the Examiner relies on unsupported, conclusory statements such as "Becker teaches that administration of any Aβ antibody would be useful to treat Alzheimer's disease," and uses the instant specification as a blueprint for the rationale to choose among elements of the prior art to arrive the instant claims. Such hindsight reconstruction is improper. For this reason additionally, the rejection of the claims as obvious over the combination of Becker and Audia should be withdrawn.

For at least the reasons set forth above, the claims are not obvious over Becker and Audia. Reconsideration of the claims and withdrawal of the rejection under section 103 over Becker and Audia is requested.

Claims 14, 19, 20, 25, 55, 56, 93-98 and 105-108 are rejected as obvious over Becker, further in view of Audia as evidenced by Johnson-Wood, et al., *Proc. Natl. Acad. Sci. USA* (1997) ("Johnson-Wood"). The Examiner states that the rejection is "virtually identical" to the rejection of the claims as obvious over Becker in view of Audia that is discussed and addressed

immediately above. To the extent that the rejection is "virtually identical" to the rejection based on Becker and Audia, the arguments set out above apply equally well and the rejection is not well taken. Accordingly, for at least the reasons set out above, claims 14, 19, 20, 25, 55, 56, 93-98 and 105-108 are not obvious over the combination of Becker in view of Audia as evidenced by Johnson-Wood, and the instant rejection should be withdrawn.

Additionally, it is noted that the Examiner cites Johnson-Wood for the proposition that antibody 3D6 "binds to amyloid plaques very well" and that this "guides the artisan of ordinary skill to select 3D6 based on its superior ability to bind the plaques known to be associated with Alzheimer's disease." Office Action at page 8. The Examiner's statement underscores the fact that it would not have been obvious to treat Alzheimer's disease with a free-end specific antibody that binds to soluble Aβ in the CSF because it was accepted that Aβ plaques were "associated with the neurotoxicity in Alzheimer's disease." [1]

Claims 14, 19, 20, 25, 72, 75, 99-104 and 109-120 are rejected as obvious over Becker in view of Mak et al., *Brain Res.,* 1994, 19:138-142 ("Mak"). The Examiner asserts Becker as discussed above and further asserts that Mak discloses a free-end specific antibody that is specific for the free C-terminus of Aβ1-40. The Examiner finds a rationale to use Mak's antibody that is allegedly specific for the free C-terminus of Aβ1-40 in the methods of Becker because "Mak teaches that said antibodies are highly specific for Aβ1-40, that this peptide is involved in the neuropathology of Alzheimer's disease, and that this peptide is the major species present in the CSF of Alzheimer's patients (*see* p. 138, first paragraph)." Office Action at page 11.

The Examiner's stated basis for the instant rejection is not believed to be well taken, as it overstates the teaching of both Becker and Mak. As discussed at length above, a fair reading of Becker shows that Becker is concerned only with the therapeutic use of conformationally-specific antibodies that are specific for Aβ that is predominantly in the β-sheet configuration and, moreover,

[1] Applicant's statements are not to be taken as indicating that antibody 3D6 does or does not bind soluble Aβ. The instant rejection is predicated on the prior art of record, which Applicant believes does not contain any indication that 3D6 antibody binds soluble Aβ. To remove any doubt, Applicant is of the understanding that antibody 3D6 does in fact bind to Aβ that is soluble in CSF. This property is inherent to 3D6, however, and was not appreciated in the prior art. The inherent, unappreciated property that antibody 3D6 binds to soluble Aβ is irrelevant to a rejection under section 103. MPEP 2141.02 Part V. ("Obviousness cannot be predicated on what is not known at the time the invention is made, even if the inherency of a certain feature is later established." *Citing In re Rijckaert,* 9 F.2d 1531, 1534 (Fed. Cir. 1993) (*quoting In re Spormann,* 363 F.2d 444, 448 (CCPA 1966)).

that such antibodies are present in neuritic plaques. It is thus overreaching on the part of the Examiner to conclude that Becker suggests the use of any antibody to treat Alzheimer's disease.

The Examiner also overstates the disclosure of Mak. The portion of Mak cited by the Examiner (page 138, first paragraph), merely states that Aβ1-40 is the major species present in CSF. Contrary to the Examiner's rationale in setting forth the instant rejection, Mak contains no suggestion that Aβ1-40 "is involved in the neuropathology of Alzheimer's disease." To the contrary, the text cited by the Examiner reiterates that Aβ1-42 "tends to aggregate, is not readily cleared and accumulates in cells." *Id.* This disclosure reflects the art-accepted view that neuritic plaques are the pathogenic agent in Alzheimer's disease and that the Aβ1-42 predominates in plaques. None of the text in Mak cited by the Examiner, however, suggests that soluble Aβ1-40 plays a role in the pathology of Alzheimer's disease or that a free-end specific antibody to the free C-terminus of Aβ1-40 could or should be used in a method to treat Alzheimer's disease by contacting the antibody with soluble Aβ in the CSF. Nor does the remainder of Mak suggest such a method.

Accordingly, neither Becker nor Mak, either alone or in combination, provides any rationale to substitute Mak's antibody in Becker's asserted methods for treating Alzheimer's disease. In the absence of such a rationale, the Examiner could only have found the motivation to combine Becker and Mak in the instant specification. Such hindsight reconstruction is impermissible and the rejection based on Becker in view of Mak should thus be withdrawn. *In re Fritch,* 972 F.2d at 1266; *In re Lee,* 277 F.3d at 1343.

Lastly, in the time since the present application was filed, major players in the field of using therapeutic antibodies to treat Alzheimer's disease have identified the instantly-claimed methods of treating Alzheimer's disease with free end-specific antibodies to be a preferred method of treatment (compared to Becker's method) and have, additionally, taken licenses or a license-option to the subject application and any patent that might mature from it. These facts are strong objective evidence that at the time the application was filed the claimed invention was <u>not</u> obvious.

Publicly available information establishes that both Wyeth and Pfizer are actively developing methods of treating Alzheimer's disease using exogenously-administered free-end

specific antibodies. Wyeth has reported on Phase 2 trials for treatment of patients with mild to moderate Alzheimer's disease with bapineuzumab, the humanized version of antibody 3D6 that is disclosed in Audia and which is specific for the free N-terminus of amyloid β. *See* attached Exhibit A (Public Release dated 29 July 2008, entitled "Elan, Wyeth present encouraging bapineuzumab Phase 2 trial results at ICAD") and Exhibit B (confirming bapineuzumab is humanized version of 3D6). Wyeth's methods thus read on the pending claims. Wyeth and Elan identify bapineuzumab as "the lead immunotherapeutic compound being developed by Wyeth and Elan through their Alzheimer's Immunotherapy Program (AIP)." *See* Exhibit B at page 1, first paragraph.

Pfizer is conducting Phase 2 trials for treatment of patients with mild to moderate Alzheimer's disease with PF-04360365, a humanized monoclonal antibody specific for the free C-terminus of Aβ1-40. *See* attached Exhibits C (entitled, "Multiple IV Dose Study of PF-04360365 In Patients With Mild to Moderate Alzheimer's Disease") and D ("PF-04360365 is a highly selective and potent monoclonal antibody that targets the C-terminal end of the beta amyloid 1-40 peptide."). Pfizer's methods thus read on the pending claims. Among the described beneficial aspects of PF-04360365 are that it "does not bind to the Amyloid Precursor Protein, from which beta amyloid is derived, and which the body needs to function normally. This may be beneficial for the risk/benefit profile of this molecule." *See* Exhibit D at page 1, second paragraph. These benefits echo the benefits of for free-end specific antibodies that are set out in the instant specification (see page 3, lines 1-5, discussing findings that "suggest Aβ is produced as a normal function of cells" and page 19, lines 2-25 ("It will be readily appreciated by those of skill in that the introduction/administration of free end specific molecules will not interfere with the normal biological functions of APP or sAPP that are not associated with the formation of Aβ peptides.)) but which were not appreciated in the field of therapeutic antibodies when the application was filed.

The statements by Wyeth and Elan (identifying the free-end specific antibody bapineuzumab as their "lead therapeutic compound" for treatment of Alzheimer's disease) and of and Pfizer (stating explicitly that the free end-specificity of PF-04360365 "may be beneficial for the risk/benefit profile of this molecule") and the commencement of clinical trials with these free end-specific antibodies, rather than any other antibodies, provide evidence that treatment of Alzheimer's disease with free-end specific antibodies is highly preferred as compared to methods of treating

Alzheimer's disease with other types of antibodies, such as disclosed in Becker, that are not free-end specific. At the time the application was filed, the prior art failed to include any suggestion that a free-end specific antibody would be superior for treating Alzheimer's disease, compared to Becker's antibody that was specific for the β-sheet conformer of Aβ. Nor has the Examiner provided any rationale to suggest that at the time the application was filed one of ordinary skill in the art would have considered free end-specific antibodies to be superior to Becker's antibodies. The finding that free end-specific antibodies are superior to Becker's antibodies for treating Alzheimer's disease establishes that the claimed invention exhibits surprising and unexpected results compared to the closest prior art. Such results are strong evidence that the claimed invention is not obvious over the prior art. *In re Soni,* 54 F.3d 746 (Fed. Cir. 1995); *Knoll Pharmaceutical Co. v. Teva Pharmaceuticals USA, Inc.,* 367 F.3d 1381 (Fed. Cir. 2004).[2]

With respect to licenses, submitted herewith is a Declaration of the inventor, Daniel G. Chain, under 37 C.F.R. §1.132 ("the Chain Declaration") which reports that Wyeth, Elan and a third anonymous major pharmaceutical company have licensed the claimed invention to treating Alzheimer's disease with free end-specific antibodies that are specific for the free N-terminus of Aβ (Wyeth and Elan) or the free C-terminus of Aβ1-40 (anonymous company), and that GSK has taken an option to license the claimed invention. The licensing of the claimed invention by erstwhile competitors and potential infringers is strong evidence that the claims are not obvious. *Minnesota Mining & Manufacturing Co. v. Johnson & Johnson Orthopaedics, Inc.,* 976 F.2d 1559,1575 (Fed. Cir. 1992) ("such real world considerations provide a colorful picture of the state of the art, what was known by those in the art, and a solid evidentiary foundation on which to rest a nonobviousness determination."; *WMS Gaming, Inc. v. International Game Technology,* 184 F.3d 1339, 1360 (Fed. Cir.1999) (finding no clear error in district courts finding that "these licenses under the [patent] are strong indicia that the patent is not obvious"). The licenses granted under the subject application, even before it has issued as a patent, are additional strong, objective evidence that the claimed invention is not obvious.

[2] It is noted that unexpected results are properly measured solely against the disclosure of Becker. *See* MPEP, Section 716.02(e).III., explaining that "applicant is not required to compare the claimed invention with subject matter that does not exist in the prior art," *citing In re Geiger,* 815 F.2d 686, 689 (Fed. Cir. 1987) (Newman, J., concurring) and *In re Chapman,* 357 F.2d 418, 422 (CCPA 1966).

For all of the reasons set out above, the pending claims are not obvious over the prior art of record. Reconsideration of the claims and withdrawal of all rejections under section 103 is requested.

IV. Conclusion

This application was filed on February 28, 2002 and has thus been pending for over seven years. Prior to the Office Action to which this Amendment responds, Applicant received and responded to six substantive Office Actions that collectively set forth rejections based on an alleged failure of entitlement to priority date, alleged lack of written description, alleged lack of enablement and prior art. All prior rejections had been overcome, most recently by filing a Pre-Appeal Brief Conference Request that received favorable consideration and was successful in overcoming all pending rejections. After more than seven years of prosecution, the present Office Action (dated May 27, 2009) set forth additional rejections based on newly-cited prior art, all of which was available to the Examiner when the first substantive Office Action was issued on February 10, 2005. For the reasons set out above, the claims are not obvious over this newly-cited prior art.

All rejections have been addressed and overcome. This application is in condition for allowance, which is earnestly solicited.

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Exhibit A

Elan, Wyeth present encouraging bapineuzumab Phase 2 trail results at ICAD

Public release date: 29-Jul-2008
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Elan, Wyeth present encouraging bapineuzumab Phase 2 trial results at ICAD

Chicago, Ill. – July 29, 2008 – Elan Corporation, plc (NYSE: ELN) and Wyeth (NYSE: WYE) today are presenting detailed results from the companies' 18-month Phase 2 study of bapineuzumab (AAB-001) in patients with mild to moderate Alzheimer's disease at the Alzheimer's Association's International Conference on Alzheimer's Disease 2008 in Chicago, Illinois. As previously announced, in the study, bapineuzumab appeared to have an acceptable safety profile and clinical activity in treating Alzheimer's disease. Potential efficacy signals were seen at a range of doses without a clear dose response. The study did not attain statistical significance on the pre-specified efficacy endpoints in the overall study population. Post-hoc analyses showed statistically significant and clinically meaningful benefits in important subgroups.

The data will be presented by Sid Gilman, M.D., William J. Herdman Distinguished University Professor of Neurology, Director of Michigan Alzheimer's Disease Research Center, University of Michigan, and Chair of the independent safety monitoring committee for bapineuzumab.

"This study was limited in its size, design and goals," said Dr. Gilman, "but if the findings seen in these post-hoc analyses are replicated in the global Phase 3 program, it would be a validation of the amyloid hypothesis and could change how physicians approach the treatment of Alzheimer's disease."

Elan and Wyeth believe that the safety and efficacy findings from this Phase 2 trial of bapineuzumab in patients with mild-to-moderate Alzheimer's disease support the design of the ongoing global Phase 3 program and plan to incorporate learnings from this study into the Phase 3 program. The companies will continue to work diligently to develop much needed new treatment options for patients and physicians.

About the Phase 2 Clinical Trial

The double-blind, placebo-controlled multiple ascending dose trial was designed to assess the safety and tolerability of bapineuzumab in mild-to-moderate Alzheimer's disease and to explore efficacy at a range of doses. Two-hundred-thirty-four (234) patients were randomized to receive one of four doses of bapineuzumab (0.15 mg/kg [n=31], 0.5 mg/kg [n=33], 1.0 mg/kg [n=30] or 2.0 mg/kg [n=30]) or placebo [n=110] by intravenous infusion every 13 weeks. Findings were reported for 229 patients in a modified intent-to-treat (MITT) analysis. Patients were intended to receive up to six doses during the 18-month study.

The pre-specified primary efficacy endpoints were change from baseline in Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog) and Disability Assessment Scale for Dementia (DAD) in the 0.5 mg/kg, 1.0 mg/kg and 2.0 mg/kg dose groups against their placebo cohorts. Other efficacy measures included change in concentrations of tau in cerebral spinal fluid (CSF), the Neuropsychological Test Battery (NTB), the Clinical Dementia Rating Sum of Boxes (CDR-SOB), the Mini Mental State Examination (MMSE) and brain volume as

measured by MRI. Efficacy was assessed from baseline for 78 weeks.

Pre-Specified Efficacy Analysis:

In the total study population, statistical significance was not obtained on the pre-specified efficacy endpoints of ADAS-cog and DAD.

Post-Hoc Efficacy Analyses:

Modified Intent to Treat (MITT) included patients who received at least one infusion and one efficacy assessment. In analyzing the data, the following were taken into account: an assumption of non linearity of the data over time, ApoE4 carrier status, and baseline MMSE and test scores.

The clinical relevance of the results for patients receiving the full 18 months of therapy was analyzed in a completer analysis. The patients included in the completer analysis received six (6) infusions and a week 78 efficacy assessment.

Using these assumptions, trends in favor of bapineuzumab treated patients were observed in ADAS-cog and NTB in the total MITT population. Additional completer analyses reinforced these trends.

The study revealed important differences in the rate of vasogenic edema by carrier status and for this reason the total population was analyzed by ApoE4 carrier status .

ApoE4 Non-Carrier Population

In the ApoE4 non-carrier patients, statistically significant differences from baseline to week 78 were observed in favor of bapineuzumab treated patients on both cognitive and functional efficacy endpoints:

- ADAS-cog treatment difference of 5.0; p=0.026
- NTB treatment difference of 0.35; p=0.006
- CDR-SB treatment difference of 1.5; p=0.040

A favorable directional change of 6.9, p>0.10 for DAD was observed.

The completer analysis for non-carrier patients was consistent with the above findings.

Additionally, in these non-carrier patients, MRI results showed significantly less brain volume reduction versus placebo, as measured by the Brain Boundary Shift Integral (BBSI), at 71 weeks , with a treatment difference of 10.7 cc; p=0.004. Smaller increases in ventricular volume (VBSI) in bapineuzumab treated patients compared to placebo were observed, which were not statistically significant. Progression of Alzheimer's disease is generally associated with loss in brain volume and increases in ventricular volume.

ApoE4 Carrier Population

In the ApoE4 carrier patients, no statistically significant changes were observed in any of the cognitive or functional efficacy endpoints. The completer analysis for the carrier population showed favorable directional changes on cognitive and functional endpoints. The ongoing Phase 3 studies in ApoE4 carriers will help clarify these findings.

MRI findings in the carrier patients showed no significant change in brain volume between bapineuzumab treated and placebo patients, while a significant increase in ventricular volume

in treated patients was observed, mean 2.5cc; p=0.037. The clinical relevance of this finding is still unclear and will continue to be evaluated.

"The clinically significant benefit seen with bapineuzumab treatment in the ApoE4 non-carrier subgroup is encouraging," said Dale Schenk, Ph.D., Executive Vice President and Chief Scientific Officer of Elan. "These results across multiple endpoints are consistent with what we have seen for beta amyloid immunotherapy from animal studies through to the patients."

"These data represent scientific validation of our decision to move rapidly into Phase 3 last year," said Gary L. Stiles, M.D., Chief Medical Officer, Wyeth. "In our Phase 3 program, we will learn much more since we will be able to study bapineuzumab in larger patient populations and better assess the results in ApoE4 carriers and non-carriers in separate trials. We are encouraged by these results and we'll achieve greater insight as we move forward."

Safety Findings

Adverse Events (AE) were observed in 95% of bapineuzumab treated patients versus 90% of placebo treated patients. AEs were generally mild to moderate and transient. With the exception of vasogenic edema, AEs did not appear to be dose related.

Adverse events seen in greater than 5% of bapineuzumab treated patients and at twice the rate of placebo treated patients were: back pain; anxiety; vomiting; vasogenic edema; hypertension; weight loss; paranoia; skin laceration; gait disturbance; and muscle spasm.

Three deaths occurred in bapineuzumab-treated patients, though these were not considered by the investigators to be treatment related. No deaths were reported in the placebo group. Other adverse events of interest occurring in less than five percent of patients treated with bapineuzumab included cataract, deep vein thrombosis, syncope, seizures and pulmonary embolism.

Vasogenic Edema (VE)

Twelve (12) cases of vasogenic edema were reported, all in treated patients, and all resolved over time. Ten (10) of these cases were reported in ApoE4 carriers with 2 cases in ApoE4 non-carriers. Eight (8) of the 12 cases were reported in the highest dose group, including both cases seen in ApoE4 non-carriers. Six (6) of the 12 cases were not associated with clinical symptoms and were detected on routine MRI scan. One (1) patient was treated with steroids. Re-dosing was instituted in six (6) of the 12 patients and no recurrence of VE was observed.

Phase 3 Program Implications

The Phase 2 data reinforce the design of the ongoing Phase 3 studies by ApoE4 carrier and non-carrier populations and the selected dose groups. The companies plan to continue all four ongoing Phase 3 studies. The ApoE4 carrier dose in the Phase 3 trials was selected to seek to minimize the risk of VE observed in the Phase 2 trial. The companies intend to obtain feedback from regulatory authorities in the coming months to finalize parameters for the Phase 3 program and discuss and reach agreement on requirements for registration.

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Investor Webcast

The Companies will host a webcast on July 29, 2008 from 6:00pm CDT (7:00pm EDT) to discuss the results of the Phase 2 clinical trial.

Participants who will discuss the trial results and field questions will include:

- Ron Black, M.D., Wyeth Research, Assistant Vice President, Neuroscience
- Sid Gilman, M.D., F.R.C.P., University of Michigan, Chair of Bapineuzumab Safety Monitoring Committee
- Allison Hulme, Ph.D., Elan, Executive Vice President and Head of Global Development
- Dale Schenk, Ph.D., Elan, Executive Vice President and Chief Scientific Officer
- Gary L. Stiles, M.D., Wyeth, Chief Medical Officer

Live audio of the webcast will be simultaneously broadcast over the Internet. The webcast can be accessed by visiting the companies' web sites at www.elan.com or www.wyeth.com and clicking on the "Investor Relations" icon. Following the live webcast, an archived version, including the slides, will be available at the same URLs.

About Bapineuzumab

Bapineuzumab is the first humanized monoclonal antibody in late-stage investigation as a potential treatment for Alzheimer's disease. Bapineuzumab is designed to clear toxic beta amyloid from the brain. The beta amyloid protein is a key component of the neuritic plaques that are implicated in the pathology of Alzheimer's disease. A global, 4,100 patient Phase 3 clinical program was initiated in December 2007 and is intended to provide safety and efficacy data to support the filing and approval of licensing applications for bapineuzumab as a potential treatment for patients with mild to moderate Alzheimer's disease. To learn more about this enrollment, patients or caregivers should contact clinical sites directly. Participating clinical sites can be found by visiting www.icarastudy.com or, in the United States by calling 1 (888) 818-MEMORY. Study site details also can be found by visiting www.clinicaltrials.gov.

About Alzheimer's Disease

Alzheimer's disease is a progressive brain disorder that gradually destroys a person's memory and ability to learn, reason, make judgments, communicate and carry out daily activities, such as bathing and eating. As Alzheimer's disease progresses, individuals may also experience changes in personality and behavior, such as anxiety, suspiciousness or agitation, as well as delusions or hallucinations. As many as 5 million Americans are estimated to have Alzheimer's disease, and more than 26 million people worldwide. One in eight baby boomers, and half of all people over 85, will develop the disease.

About the Elan and Wyeth Collaboration

The Wyeth and Elan Alzheimer's Immunotherapy Program (AIP) includes investigational clinical programs for bapineuzumab. AIP is a collaboration between the two companies to research, develop and commercialize immunotherapeutic approaches that may be used to treat and possibly prevent the onset of Alzheimer's disease. AIP research focuses on the beta amyloid hypothesis, as the companies believe that enhancing the clearance of beta amyloid in the brain may provide a new treatment approach for Alzheimer's disease.

About Elan

Elan Corporation, plc is a neuroscience-based biotechnology company committed to making a difference in the lives of patients and their families by dedicating itself to bringing innovations in science to fill significant unmet medical needs that continue to exist around the world. Elan shares trade on the New York, London and Dublin Stock Exchanges. For additional information about the company, please visit http://www.elan.com.

About Wyeth

Wyeth Pharmaceuticals, a division of Wyeth, has leading products in the areas of women's health care, infectious disease, gastrointestinal health, central nervous system, inflammation, transplantation, hemophilia, oncology, vaccines and nutritional products.

Wyeth is one of the world's largest research-driven pharmaceutical and health care products companies. It is a leader in the discovery, development, manufacturing and marketing of pharmaceuticals, vaccines, biotechnology products, nutritionals and non-prescription medicines that improve the quality of life for people worldwide. The Company's major divisions include Wyeth Pharmaceuticals, Wyeth Consumer Healthcare and Fort Dodge Animal Health. For additional information about the company, please visit http://www.wyeth.com.

Safe Harbor/Forward-Looking Statements

The statements in this press release and on the related webcast regarding the companies' assessment of the Phase 2 data and its implications for the Phase 3 program and future development of bapineuzumab are forward-looking statements that are subject to risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements. In particular, these statements are subject to the risk that further analyses of the Phase 2 data may lead to different (including less favorable) interpretations of the data than the analyses conducted to date and/or may identify important implications of the Phase 2 data that are not reflected in these statements. Clinical trial data are subject to differing interpretations, and regulatory agencies, medical and scientific experts and others may not share the companies' views of the Phase 2 data or its implications for the Phase 3 program and future development of bapineuzumab. In addition, further analyses of the Phase 2 data and discussion with regulatory authorities may lead to important modifications to the Phase 3 program. There can be no assurance that the clinical program for bapineuzumab will be successful in demonstrating safety and/or efficacy, that we will not encounter problems or delays in clinical development, or that bapineuzumab will ever receive regulatory approval or be successfully commercialized. Other risks and uncertainties that could cause actual results to differ materially from those expressed or implied by these forward-looking statements include those detailed from time to time in the Companies' periodic reports filed with the Securities and Exchange Commission, including Wyeth's current reports on Form 8-K, quarterly reports on Form 10-Q and annual report on Form 10-K, particularly the discussion under the caption "Item 1A, Risk Factors" in Wyeth's Annual Report on Form 10-K for the year ended December 31, 2007, which was filed with the Securities and Exchange Commission on February 29, 2008, and Elan's Reports of Foreign Issuer on Form 6-K and Annual Report on Form 20-F, particularly the discussion under the caption "Item 3D, Risk Factors" in Elan's Annual Report on Form 20-F for the year ended December 31, 2007, which was filed with the Securities and Exchange Commission on February 28, 2008. The forward-looking statements in this press release are qualified by these risk factors. We assume no obligation to publicly update any forward-looking statements, whether as a result of new information, future developments or otherwise.

Exhibit B

Bapineuzumab (AAB-001) Backgrounder Understanding the Clinical Potential and Research Program

Elan Wyeth

Bapineuzumab (AAB-001) Backgrounder
Understanding the Clinical Potential and Research Program

What is Bapineuzumab?

Bapineuzumab (AAB-001) is the lead immunotherapeutic compound being developed by Wyeth and Elan through their Alzheimer's Immunotherapy Program (AIP).

Bapineuzumab has been designed to clear toxic beta amyloid from the brain, and its potential ability to do this is currently being evaluated. Beta amyloid is a component of the neuritic plaques that are implicated in the pathology of Alzheimer's disease. Based on evidence from animal studies with the non-humanized mouse version of bapineuzumab (known as 3D6), the companies are investigating whether this mode of action may slow or prevent the progressive neurodegeneration in the brain associated with Alzheimer's disease.

Bapineuzumab is a humanized monoclonal antibody that provides patients with an antibody to beta amyloid. Bapineuzumab is not a vaccine; it is an infusion product that does not require patients to mount their own immune response and generate their own antibodies. Wyeth and Elan have received fast track designation from the U.S. Food and Drug Administration (FDA) for the review of bapineuzumab as a potential treatment of patients with mild to moderate Alzheimer's disease.

Early Preclinical & Clinical Findings

In animal studies with the non-humanized mouse version of bapineuzumab (known as 3D6), the compound was shown to clear beta amyloid from the brain.

In a Phase 1 safety and tolerability study of 30 patients, although the overall number of treatment-emergent adverse events was similar among the bapineuzumab-treated and placebo-treated groups, serious treatment-related adverse events were more common in the highest bapineuzumab dose group (5 mg/kg). These serious adverse events included retinal vascular disorder and cerebral vasogenic edema. This dose is no longer being studied. The safety and tolerability of bapineuzumab continue to be evaluated in the ongoing Phase 2 and Phase 3 programs. The results from this Phase 1 study supported the decision to initiate a bapineuzumab multiple ascending dose study in patients with mild to moderate Alzheimer's disease.

Bapineuzumab Phase 2 and Phase 3 Clinical Trial Programs

Mid- and late-stage clinical trials of bapineuzumab include a Phase 2 multiple ascending dose study, a Phase 2 imaging study, and a global Phase 3 clinical program. These programs are collectively designed to assess the safety, tolerability, and efficacy of bapineuzumab in treating patients with mild to moderate Alzheimer's disease.

Phase 2 Multiple-Ascending Dose Trial

The Phase 2 multiple ascending dose trial assessed the dosing, safety, efficacy, tolerability, pharmacokinetics, pharmacodynamics, and immunogenicity of bapineuzumab in patients with mild to moderate Alzheimer's disease. Additional objectives included measurement of biomarkers that may be supportive of the efficacy of bapineuzumab. The trial also collected information that helped in the design of the pivotal Phase 3 trials.

Design	• Randomized, double-blind, placebo-controlled, multiple ascending dose study
Safety Objective	• To assess the safety and tolerability of bapineuzumab in patients with mild to moderate Alzheimer's disease
Patients	• 240 total participants with mild to moderate Alzheimer's disease; participants were divided into four bapineuzumab dosing cohorts plus a placebo arm
Estimated Study Duration	• Approximately 123 weeks (including a 6-week screening period, 65 weeks of dosing, and 52 weeks for follow-up) for each patient's participation
Dosing	• 0.15 mg/kg, 0.5 mg/kg, 1 mg/kg, and 2 mg/kg; each participant received an infusion every 13 weeks for a total of 6 doses over the course of the study
Co-Primary Efficacy End Points	• Changes from screening scores on the Alzheimer's Disease Assessment Scale – Cognitive Subscale and Disability Assessment Scale for Dementia
Secondary Efficacy End Point	• Effect of bapineuzumab on a biomarker that may be indicative of disease modification
Other End Points	• Changes from screening scores on the Neuropsychological Test Battery, Clinical Dementia Rating Sum of Boxes, and Mini Mental State Examination

The Phase 2 imaging study, expected to be completed in early 2009, is using a technique called PET-PIB to assess the amount of amyloid plaque in the brains of patients treated with bapineuzumab.

Phase 3 Clinical Program

In May 2007, Wyeth and Elan announced plans to initiate a Phase 3 clinical program with bapineuzumab for the treatment of patients with mild to moderate Alzheimer's disease.

This Phase 3 clinical program is intended to evaluate the safety and efficacy of bapineuzumab as a potential treatment for patients with mild to moderate Alzheimer's disease. Bapineuzumab is believed to be the first humanized monoclonal antibody in late-stage investigation as a potential treatment for patients with mild to moderate Alzheimer's disease.

The Phase 3 clinical program is expected to include four randomized, double-blind, placebo-controlled studies in approximately 4,100 total patients with mild to moderate Alzheimer's disease. More than 350 sites worldwide are expected to participate in the program. Patients are planned to be distributed equally between North American and international sites.

Each of the four studies will have co-primary efficacy end points — one cognitive and one functional. Patients will participate for 18 months and will be evaluated using several methods, including neuropsychiatric scales, imaging and biomarker analysis.

Design	• Randomized, double-blind, placebo-controlled, parallel-group, studies • Two studies of participants who carry the apolipoprotein E

	(ApoE4) allele, a known genetic risk factor of Alzheimer's disease, and two studies in non-carriers
Safety Objective	• To assess the safety of multiple doses of intravenously administered bapineuzumab in patients with mild to moderate Alzheimer's disease versus placebo
Patients	• Approximately 4,100 patients with mild to moderate Alzheimer's disease
Estimated Study Duration	• Approximately 83 weeks (including a 5-week screening period, 65 weeks of dosing, and 13 weeks for follow-up) for each patient's participation; the entire study duration is expected to take approximately 135 weeks from the first visit of the first patient (screening) to the last visit of the last patient
Dosing	• 0.5 mg/kg, 1 mg/kg, and 2 mg/kg in non-carriers and 0.5 mg/kg in ApoE4 carriers by infusion every 13 weeks for a total of six infusions over the course of the study
Co-Primary Efficacy End Points	• Change from baseline scores for the Neuropsychological Test Battery and the Disability Assessment Scale for Dementia up to week 78
Key Secondary Efficacy End Points	• Change from baseline scores for the Alzheimer's Disease Assessment Scale – Cognitive Subscale and the Clinical Dementia Rating Sum of Boxes up to week 78
Other End Points	• Change from baseline scores on the Neuropsychiatric Inventory, the Mini Mental State Examination, whole brain volume, ventricular volume, ventricular boundary shift integral, population pharmacokinetic profile and parameter estimates, pharmacodynamic profile, the immunogenicity of doses, the Dependence Scale, and the Resource Utilization in Dementia, Quality of Life and Health Utilities Index

To learn more about enrollment, patients or caregivers should contact clinical sites directly. Participating North American study sites can be found by calling +1 (888) 818-MEMORY or by visiting www.icarastudy.com. Participating international clinical sites can be found by visiting www.globalicarastudy.com. Site details for North American and international studies also can be found by visiting www.clinicaltrials.gov.

Assessment Scales
The AIP intends to use several clinical trial measurement tools to evaluate memory, function, and dependence to characterize the potential of bapineuzumab as a treatment for patients with mild to moderate Alzheimer's disease.

- *Neuropsychological Test Battery*
  - A cognitive assessment scale that combines six cognitive tests, yielding nine measures of patient performance
  - Has been shown to measure both memory and executive function

- *Alzheimer's Disease Assessment Scale - Cognitive Subscale*
  - A scale to evaluate the severity of cognitive behavioral dysfunctions characteristic of persons with Alzheimer's disease
  - It consists of tasks measuring the disturbances of memory, language, praxis, attention and other cognitive abilities

- *Disability Assessment in Dementia*
  - A measurement of instrumental and basic activities of daily living, which is completed by the Alzheimer's patient's caregiver to measure a patient's performance on basic activity of daily living
  - Performance on basic activities of daily living are evaluated in ten aspects including, hygiene, dressing, continence, eating, meal preparation, telephoning, going on an outing, finance, and correspondence. For each activity, questions are asked to evaluate patient's performance on initiation, planning and organization, and effectiveness

- *Clinical Dementia Rating – Sum of Boxes (CDR-SOB) Scale*
  - A global rating scale designed for use in staging dementia. It scores deficits in cognitive end function domains
  - Sum of six clinical ratings including: 1) memory, 2) orientation, 3) judgment and problem solving, 4) home and hobbies, 5) involvement in community affairs, and 6) personal care based on the Clinical Dementia Rating Scale

- *Dependence Scale*
  - A caregiver rated instrument for determining the extent to which persons with Alzheimer's disease are dependent on others
  - The scale measures the disease impact on patients and caregivers using 13 questions such as, "Does the patient need reminders or advice to manage chores, do shopping, cooking, play games, or handle money?" and "Does the patient need to be tube fed?"

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Exhibit C

Multiple IV Dose Study Of PF-04360365 In Patients With Mild To Moderate Alzheimer's Disease

Multiple IV Dose Study Of PF-04360365 In Patients With Mild To Moderate Alzheimer's Disease

This study is ongoing, but not recruiting participants.

First Received: July 23, 2008 Last Updated: July 13, 2009 History of Changes

Sponsored by:	**Pfizer**
Information provided by:	Pfizer
ClinicalTrials.gov Identifier:	NCT00722046

Purpose

Purpose of the study is to determine whether multiple dose administration of PF-04360365 is safe and well tolerated in patient with mild to moderate Alzheimer's disease.

Condition	Intervention	Phase
Alzheimer's Disease	Biological: PF-04360365 0.1 mg/kg Biological: PF-04360365 0.5 mg/kg Biological: PF-04360365 1 mg/kg Drug: Placebo Biological: PF-04360365 3 mg/kg Biological: PF-04360365 8.5 mg/kg	Phase II

Study Type: Interventional
Study Design: Treatment, Randomized, Double Blind (Subject, Caregiver, Investigator), Parallel Assignment, Safety Study

Official Title: A Phase 2 Multicenter, Randomized, Double Blind, Placebo-Controlled Study Of The Safety, Tolerability, And Pharmacokinetics Of Multiple Doses Of PF-04360365 In Patients With Mild To Moderate Alzheimer's Disease

Resource links provided by NLM:

Genetics Home Reference related topics: Alzheimer disease

MedlinePlus related topics: Alzheimer's Disease

U.S. FDA Resources

Further study details as provided by Pfizer:

Primary Outcome Measures:

- Safety/tolerability of PF-04360365 in subjects with mild to moderate Alzheimer's disease dosed for 18 months. (adverse events, physical/neurologic exams, vital signs, 12-lead ECG, clinical labs, brain MRI, cognitive assessments) [Time Frame: 24 months] [Designated as safety issue: No]
- Pharmacokinetics of PF-04360365 following administration of multiple doses in subjects with mild to moderate Alzheimer's disease. (plasma and cerebrospinal fluid (as available) PF-04360365 concentrations) [Time Frame: 24 months] [Designated as safety issue: No]

Secondary Outcome Measures:

- Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog); Disability Assessment for Dementia (DAD); plasma/CSF Abeta; CSF tau and phosphotau; CSF protein, RBCs, WBCs and glucose; Immunogenicity (anti-drug antibodies) [Time Frame: 24 months] [Designated as safety issue: No]

Estimated Enrollment:	175
Study Start Date:	December 2008
Estimated Study Completion Date:	November 2011
Estimated Primary Completion Date:	November 2011 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
PF-04360365 0.1 mg/kg: Experimental	Biological: PF-04360365 0.1 mg/kg 0.1 mg/kg every 60 days (10 doses total)
PF-04360365 0.5 mg/kg: Experimental	Biological: PF-04360365 0.5 mg/kg 0.5 mg/kg every 60 days (10 doses total)
PF-04360365 1 mg/kg: Experimental	Biological: PF-04360365 1 mg/kg 1 mg/kg every 60 days (10 doses total)
Placebo: Placebo Comparator	Drug: Placebo Placebo every 60 days (10 doses total)
PF-04360365 3 mg/kg: Experimental	Biological: PF-04360365 3 mg/kg 3 mg/kg every 60 days (10 doses total)
PF-04360365 8.5 mg/kg: Experimental	Biological: PF-04360365 8.5 mg/kg 8.5 mg/kg every 60 days (10 doses total)

Eligibility

Ages Eligible for Study:	50 Years and older
Genders Eligible for Study:	Both
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:

- Males or females of non childbearing potential, age > or = 50
- Diagnosis of probable Alzheimer's disease, consistent with criterial from both:

  - National Institute of Neurological and Communicable Disease and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)
  - Diagnostic and Statistical Manual of Mental Disorders (DSM IV)
- Mini-mental status exam score of 16-26 inclusive
- Rosen-Modified Hachinski Ischemia Score of < or = 4

Exclusion Criteria:

- Diagnosis or history of other demential or neurodegenerative disorders
- Diagnosis or history of clinically significant cerebrovascular disease
- Specific findings on magnetic resonance imaging (MRI); cortical infarct, micro hemorrhage, multiple white matter lacunes, extensive white matter abnormalities
- History of autoimmune disorders
- History of allergic or anaphylactic reactions

Contacts and Locations

Please refer to this study by its ClinicalTrials.gov identifier: NCT00722046

Show 38 Study Locations

Sponsors and Collaborators

Pfizer

Investigators

Study Director: Pfizer CT.gov Call Center Pfizer

More Information

Additional Information:

To obtain contact information for a study center near you, click here.

No publications provided

Responsible Party:	Pfizer, Inc. (Director, Clinical Trial Disclosure Group)
Study ID Numbers:	A9951002
Study First Received:	July 23, 2008
Last Updated:	July 13, 2009
ClinicalTrials.gov Identifier:	NCT00722046 History of Changes
Health Authority:	United States: Food and Drug Administration

Keywords provided by Pfizer:
Alzheimer's disease, antibody, amyloid

Study placed in the following topic categories:

Antibodies	Brain Diseases
Delirium, Dementia, Amnestic, Cognitive Disorders	Dementia
Mental Disorders	Cognition Disorders
Alzheimer Disease	Immunoglobulins
Central Nervous System Diseases	Delirium
Neurodegenerative Diseases	

Additional relevant MeSH terms:

Delirium, Dementia, Amnestic, Cognitive	Neurodegenerative Diseases

Disorders
Mental Disorders
Nervous System Diseases
Alzheimer Disease
Central Nervous System Diseases

Tauopathies
Brain Diseases
Dementia

ClinicalTrials.gov processed this record on July 16, 2009

Exhibit D

New antibody promising in treatment of Alzheimer's disease

CHRONIC DISEASES

New antibody promising in treatment of Alzheimer's disease

Issued by: Magna Carta

New preclinical data on Pfizer's highly selective anti-amyloid monoclonal antibody shows promise in potentially changing the course of Alzheimer's.

CHICAGO— For the first time, Pfizer, Inc. released promising pre-clinical data on its investigational immunotherapy compound PF-04360365, a humanized anti-amyloid monoclonal antibody being studied for the treatment of Alzheimer's disease (AD). In this study, a single injection of PF-04360365 in genetically engineered mice reduced brain levels of beta amyloid, a protein that accumulates in the brains of those with AD, initiating a cascade of events that lead to brain cell damage and death.[i]a, 1b These data were presented today at the Alzheimer's Association 2008 International Conference on Alzheimer's Disease (ICAD).

Pfizer's PF-04360365 is a highly selective and potent monoclonal antibody that targets the C-terminal end of the beta amyloid 1-40 peptide. This means that PF-04360365 does not bind to the Amyloid Precursor Protein, from which beta amyloid is derived, and which the body needs to function normally. This may be beneficial for the risk/benefit profile of this molecule. In addition, PF-04360365 has been designed to minimize the risk of dangerous inflammation in the brain. This selectivity and design of the molecule suggest the compound may be able to safely remove beta amyloid from the brain, prevent plaque formation - a hallmark of AD - and potentially slow or halt AD disease progression. Two phase I studies of PF-04360365 are currently underway in AD patients.

"We have come a long way in understanding how people with Alzheimer's may react to various forms of immunotherapy," says Thomas Lanz, Senior Scientist at Pfizer and lead researcher of this PF-04360365 study. "This is an important area of research in the fight against Alzheimer's disease, and it's one the scientific community is optimistic about. We are glad to contribute to the body of knowledge that may one day fulfill the potential of this approach."

Preclinical Study Results

The primary study objective was to determine the effect of PF-04360365 on beta amyloid levels in the brain and blood.

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Results from this study demonstrated that treatment with a single injection of PF-04360365 significantly reduced levels of beta amyloid in the brains of mice genetically modified to overproduce amyloid and plaque buildup. In the study, beta amyloid was significantly reduced in the hippocampus, an area of the brain that impacts memory and one of the first areas of the brain to become damaged in those with AD. The compound also increased levels of beta amyloid in the blood up to 100-fold.

"Pfizer is pleased to unveil these promising data on our investigational monoclonal antibody compound as one example of our researchers' commitment and vision to lift the burden of Alzheimer's on patients and those who care for them," says Liam Ratcliffe, Senior Vice President and Development Head for Pfizer Neurosciences. "Our hope is that this compound as well as others Pfizer is exploring for Alzheimer's may one day be able to slow cognitive decline or even reverse memory loss in the patients caught in the grips of this terrible disease."

AD is a progressive disorder characterized by the gradual loss of memory and a decline in cognitive ability; changes in behavior; and a loss in ability to carry out daily activities[ii]. It places a tremendous burden on patients, those caring for them, and healthcare systems, costing the U.S. Government more than $148 billion in 2005.[iii] AD remains one of the world's most undiagnosed diseases, with only one-third of the world's approximately 18 million sufferers receiving treatment.[iv]

References

[i] Hardy J, Selkoe DJ. The Amyloid Hypothesis of Alzheimer's Disease: Progress and Problems on the Road to Therapeutics. Science. 2002;297:353-6.

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